perfused intestine–liver preparations have been developed for simultaneous study of absorption and first-pass metabolism (121,122).

3.4. Whole Animal Models (Transgenic Animals and Mutant Strains)

Animal models have been extremely useful for the study of organ transport (Table 3). Specifically, genetically deficient and mutant animal strains have been successfully utilized to identify mechanisms involved in xenobiotic transport and their effect on drug disposition and activity. The absence or malfunction of a single gene defines these animal models. Perhaps, the most significant of these strains is the MDR1-knockout mouse, a model used to study the role of Pgp in drug disposition and activity (82,123–125).

Additional mutant rat strains have been established with an inherently defective ability to excrete organic anions into bile (due to MRP2 deficiency). These include transport-deficient (TR−) and Eisai hyperbilirubinemic (EHBR) rats (126,127). Comparison between mutants and normal rats allows for study of the role of MRP2 on drug disposition (13,18).

4. HEPATOBILIARY TRANSPORT

Although widely recognized as the major site of drug biotransformation, one of the main functions of the liver is the formation of bile. Hepatobiliary transport processes contribute to the disposition of a number of endogenous substances and xenobiotics. Hepatic xenobiotic disposition involves a number of different pathways including uptake into the hepatocyte, intracellular translocation, biotransformation, and egress into blood and/or bile (77). Understanding the processes governing hepatic uptake and biliary secretion will not only permit a more accurate characterization of drug disposition in vivo, but also may allow for the development of medications specifically targeted to various regions of the liver.

4.1. Organic Cation Transport

Traditionally, organic cations were regarded as a homogenous class of compounds transported by a single transport system in the liver. Today, organic cations represent a heterogeneous group of compounds that are taken up by the liver through multiple transport systems with widely overlapping substrate specificity. Organic cations are classified into five general categories (Table 5): endogenous compounds, Type I cationic compounds, Type II cationic compounds, Pgp substrates, and cardiac glycosides. Type I compounds are relatively small, aliphatic compounds with a positively charged nitrogen group. Type II compounds are more bulky compounds with one or